Specification and provisional priority

09/928,139

THE MANUFACTURE OF SINGLE ISOMER METHYLPHENIDATE

Field of the Invention

This invention relates to an economic process for the manufacture of a single isomer of methylphenidate.

Background to the Invention

Methylphenidate is a therapeutic agent that is widely used in the treatment of attention-deficit hyperactivity disorder. It is a controlled substance.

Methylphenidate was first prepared as a mixture of the *erythro* [*R*S**] and *threo* [*R*R**] racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereoisomer. It is now considered that it is the *d-threo* [or (*R*,*R*)] enantiomer that has the preferred therapeutic activity. Uses of this enantiomer are disclosed in PCT/GB96/01688, PCT/GB96/01689 and PCT/GB96/01690, the contents of which are incorporated herein by reference.

The resolution of *threo*-methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diylhydrogen phosphate, a process first reported by Patrick *et al*, The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987). A more efficient resolution, using a *O,O'*-diaroyltartaric acid, is disclosed in PCT/GB97/00185, the contents of which are incorporated by reference; in particular, the use of *O,O'*-di-*p*-toluoyltartaric acid allows the diastereoisomeric salts to be very readily separated.

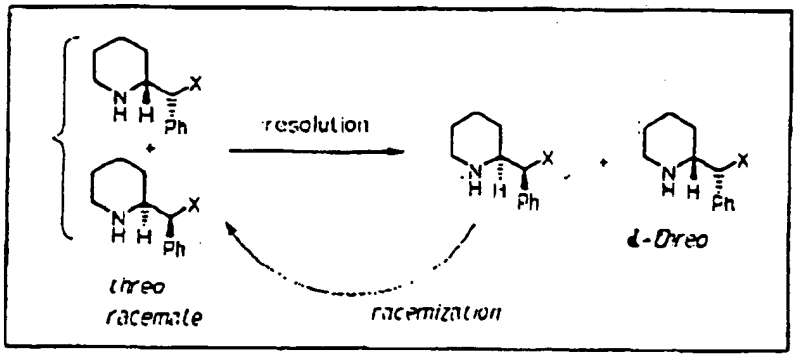
In an alternative approach, disclosed in US-A-2957880, the amide of *erythro*-methylphenidate (i.e. as $-CONH_2$ instead of $-CO_2Me$) is resolved using tartaric acid. However, this resolution must be followed by amide hydrolysis, and equilibration at the benzylic centre, to give the *threo* isomer of the carboxylic acid (ritalinic acid) which is esterified. US-A-2957880 describes a general process for conversion of *erythro* diastereoisomers to *threo* diastereoisomers, using alkali and elevated temperature.

In order to establish an economic resolution process, it is highly desirable to be able to recycle the unwanted enantiomer into the resolution by way of a racemisation. This becomes especially important when the resolution is performed late in a synthesis. An example of such a resolution and racemisation procedure is

in the case of naproxen where the single stereogenic carbon centre, which is benzylic and further activated by the carboxylate, is readily racemised. However, in the case of methylphenidate, there are two stereogenic centres. While one centre is similarly benzylic and can be epimerised as indicated in US-A-2957880, that converts the material into a mixture of two diastereoisomers and not into the racemate that is required for recycling.

Summary of the Invention

This invention is based on the discovery of methods to effect racemisation of both chiral centres of methylphenidate. This process gives an optically inactive mixture of stereoisomers in which equilibrium may favour the *threo* isomer; the result is that undesired enantiomer is converted predominantly into the racemate of the *threo* isomer which can then be reintroduced into the resolution. The overall process of a combination of resolution and racemisation that may allow complete conversion into the required isomer is outlined in Scheme 1. The *erythro* isomer that may remain after the racemisation can be separated by conventional methods such as crystallisation at this stage and subjected further to the epimerisation conditions defined below. Alternatively, it can be recycled after passage through resolution of the *threo* isomer.



Scheme 1

Description of the Invention

In Scheme 1, the group X may be the -CO_2Me function of methylphenidate. Resolution of this compound may be carried out by generally known procedures, e.g. by formation of a diastereoisomeric salt with a chiral acid. Alternatively, the resolution may be a biotransformation that modifies the group X in one enantiomer so that the enantiomers (of different compounds) are then readily separated.

This invention includes the means to effect racemisation at both stereogenic centres. It has been discovered that such racemisation can be carried out by way of activation at the piperidine nitrogen, which probably promotes a fragmentation of the ring, although the exact mechanism has not been ascertained. The putative olefinic intermediate has no chirality and recloses to a racemic mixture.

There are various ways in which the nitrogen may be activated, to promote the elimination-addition mechanism. One approach is treatment with an acid, for example a carboxylic acid, at a sufficiently high temperature, such as heating with propionic acid, e.g. under reflux. This reaction is suitably conducted in an inert solvent such as toluene. The racemisation can optionally be accelerated by the judicious addition of amounts of additives such as water or inorganic salts that will favour the charge separation in the transition state of the elimination. This reaction may also be promoted by the addition of an aldehyde or ketone (e.g. butyraldehyde or 2-cyclohexen-1-one).

As indicated above, conditions are known that will epimerise *erythro*-ritalinic acid at the benzylic centre only. On the basis of the evidence herein, it will readily be apparent to the man of ordinary skill in the art that conditions can be adopted, in order to give all 4 stereoisomers of methylphenidate, by racemisation at both chiral centres.

Following racemisation, and prior to resolution, it is necessary to enrich the mixture in the *threo* enantiomers. For example, the racemic methylphenidate is hydrolysed, e.g. using base such as alkali metal hydroxide. This can be done such that there is also epimerisation. Work-up with acid gives predominantly *threo* ritalinic acid (X = CO_2H), which can be esterified, e.g. by reaction with methanol, to give the appropriate substrate for resolution.. Alternatively, the *erythro* isomers

can be separated by precipitation, and then subjected to sequential epimerisation, esterification and resolution.

The following experiment was conducted in order to illustrate the feasibility of racemisation.

Propionic acid (2 ml) was added to a solution of *d-threo*-methylphenidate (5 g) in toluene (25 ml), and the solution was heated under reflux for 4 hours. The mixture was then cooled to ambient temperature, and was rinsed with dilute sodium carbonate and then with water. The organic phase was separated and dried with magnesium sulphate and evaporated under reduced pressure. The resulting oil (4.3 g) was analysed by chiral HPLC which indicated the presence of all 4 stereoisomers of methylphenidate in roughly equal proportions.

In order to preparing *d-threo*-methyphenidate by an efficient recycling process, the following protocol is adopted:

1) Resolve *dl-threo*-methylphenidate by the procedure described in the Example of PCT/GB97/00185.

2) Racemise the residual *l-threo*-methylphenidate by the procedure described in the experiment above.

3) Hydrolyse the resultant racemic methylphenidate using 50% KOH and heating at reflux.

4) Esterify the resultant mixture of enantiomers, enriched in *dl-threo*-ritalinic acid, by reaction with MeOH and HCl.

5) Isolate the free base and recrystallise, to obtain essentially pure *dl-threo*-methylphenidate, suitable as a feedstock for resolution into constituent enantiomers.

RESOLUTION/RACEMIZATION PROCESS

Field of the Invention

This invention relates to an economic process for the manufacture of a single isomer of methylphenidate through combining resolution with recycling of the undesired enantiomer.

Background to the Invention

Methylphenidate was first prepared as a mixture of the *erythro* [*R*S**] and *threo* [*R*R**] racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereoisomer.

The resolution of *threo* methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, a process first reported by Patrick *et al*, The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987). A more efficient resolution with *O,O'*-diaroyltartaric acids is disclosed in British Patent Application No. 9601228.1 and in US Application Serial No. 60/013,779, filed March 21, 1996, the contents of which are incorporated by reference; in particular, using *O,O'*-di-*p*-toluoyltartaric acids allows the diastereoisomeric salts to be very readily separated. In general, it is the d-*threo* [or (*R,R*)] enantiomer that is considered to have the preferred therapeutic activity.

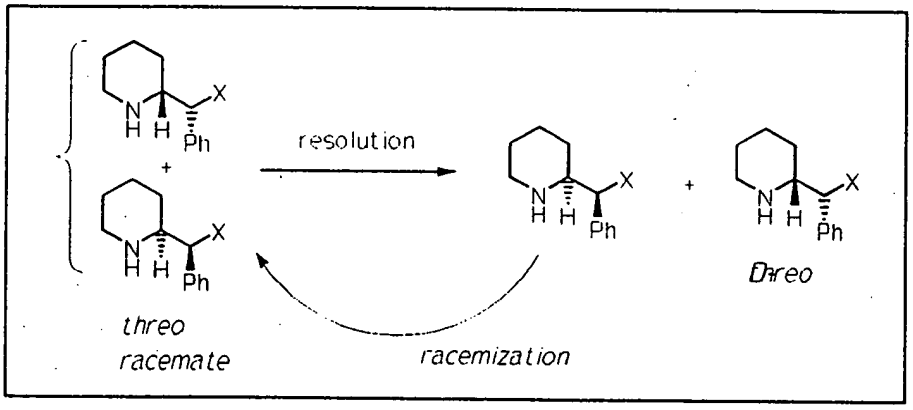
In an alternative approach disclosed in US-A-2957880, the amide of *erythro* methylphenidate (i.e. as $-CONH_2$ instead of $-CO_2Me$) is resolved with tartaric acid. Then amide hydrolysis, and equilibration at the benzylic centre, gives the *threo* isomer of the carboxylic acid which is esterified.

In order to establish an economic resolution process, it is highly desirable to be able to recycle the unwanted enantiomer into the resolution by way of a racemization. This becomes especially important when the resolution is performed late in a synthesis. An example of such a resolution and racemization procedure is in the case of naproxen where the single stereogenic carbon centre, which is benzylic and further activated by the carboxylate, is readily racemized. However, in the case of methylphenidate, there are two stereogenic centres. While one centre is similarly benzylic and can be epimerized as indicated in US-A-2957880, that converts the material into a mixture of diastereoisomers and not into the racemate that is required

for recycling. There is no method reported by which epimerization of the stereogenic centre adjacent to the piperidine nitrogen atom in methylphenidate can be effected.

Summary of the Invention

This invention is based on the novel discovery of methods to effect epimerization of *both* chiral centres in methylphenidate. Such epimerization gives a mixture of isomers in which equilibrium may favour the *threo* isomer; the result is that undesired enantiomer is converted predominantly into the racemate of the *threo* isomer which can then be reintroduced into the resolution. The overall process of a combination of resolution and racemization that may allow complete conversion into the required isomer is outlined in Scheme 1. The minor amount of *erythro* isomer that may remain after the racemization can be separated by conventional methods such as crystallization at this stage and subjected further to the epimerization conditions defined below. Alternatively, it can be recycled after passage through resolution of the *threo* isomer.

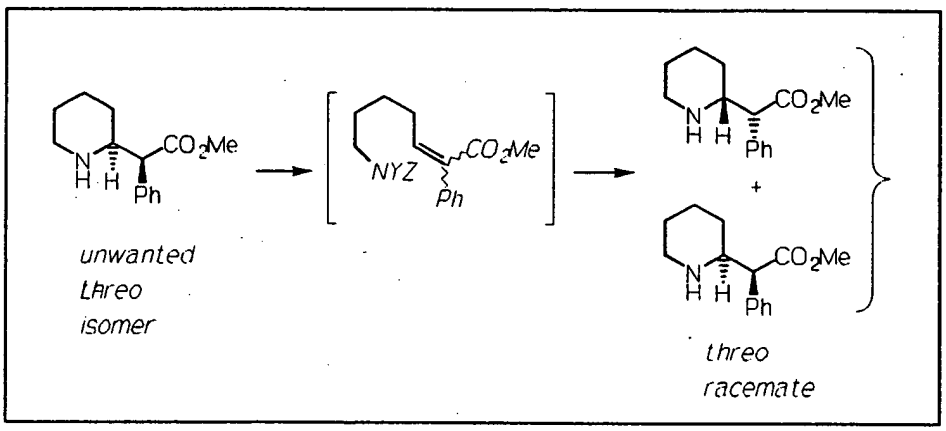


Scheme 1

In Scheme 1, the group X may be the $-CO_2Me$ function of methylphenidate and resolution carried out by known procedures, e.g. by formation of a diastereoisomeric salt with a chiral acid. Alternatively, the group X may be another resolvable function, e.g. a different ester, an amide, or a nitrile which can be converted into the methyl ester for methylphenidate. The resolution may be a

biotransformation that modifies the group X in one enantiomer so that the enantiomers are then separated.

The invention is the racemization which requires epimerization at both stereogenic centres. It has been discovered that such racemization can be carried out by way of activation at the piperidine nitrogen, to promote a fragmentation of the ring. The resultant olefinic intermediate has no chirality and recloses to a racemic mixture. Without wishing to be bound by theory, a possible mechanism is shown in Scheme 2 for the case of methylphenidate itself.



Scheme 2

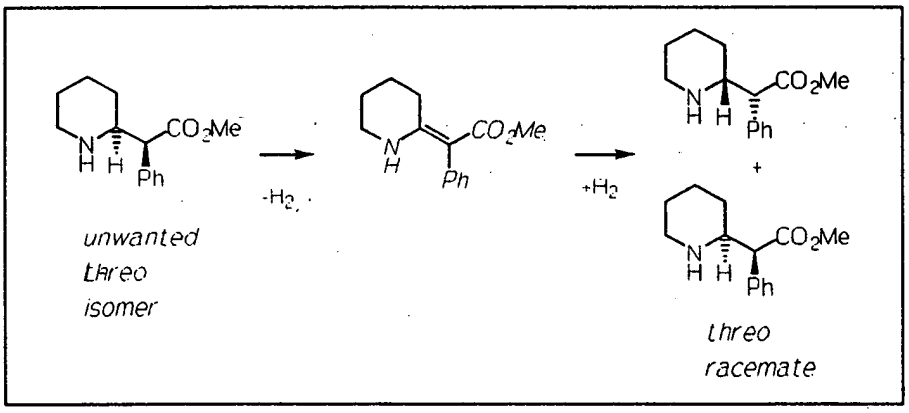
Description of the Invention

There are various ways in which the nitrogen may be activated, to promote the elimination-addition mechanism. One approach is treatment with an acid, for example a carboxylic acid, at a sufficiently high temperature, such as heating with propionic acid under reflux. This reaction is suitably conducted in an inert solvent such as toluene. The racemization can optionally be accelerated by the judicious addition of amounts of additives such as water or inorganic salts that will favour the charge separation in the transition state of the elimination.

In another method, treatment with an aldehyde or ketone (e.g. butyraldehyde or 2-cyclohexen-1-one) forms an iminium ion which, as well as activating the elimination, can render the proton at the piperidine stereogenic centre sufficiently

acidic to be removed by a base present. Thus a typical procedure involves heating the unwanted enantiomer with an aldehyde and a base in an appropriate solvent.

An alternative strategy for effecting racemization of the undesired isomer is by a dehydrogenation/hydrogenation sequence as depicted by Scheme 3. Thus, for example, the dehydrogenation may be by way of bromination at the benzylic position, followed by dehydrobromination to the olefin; this novel olefin is then hydrogenated. In this sequence, it is likely that the geometric isomer of the olefin indicated in Scheme 3 will be formed in preference because of the stabilisation provided by having the nitrogen and ester functions in a *trans* relationship. In that event, the usual *cis* hydrogenation will give the required *threo* diastereoisomer of methylphenidate. In a catalytic procedure, a catalyst is chosen that will remove and then reattach hydrogen. For example, a heterogeneous catalyst such as a transition metal adsorbed on carbon or a homogeneous catalyst such as a phosphine complex of ruthenium or rhodium may be used.



Scheme 3

The following Example illustrates the invention.

Example

Propionic acid (2 ml) was added to a solution of *d-threo* methylphenidate (5 g) in toluene (25 ml) and the solution was heated under reflux for 4 hours. The mixture was then cooled to ambient temperature and was rinsed with dilute sodium carbonate and then with water. The organic phase was separated and dried with magnesium sulphate and evaporated under reduced pressure. The resulting oil (4.3

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